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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/269,321	09/13/1999	WILLIAM KAELIN JR.	46793	9798

7590 07/14/2004

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/269,321	KAELIN JR. ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 May 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/6/1999*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/04 has been entered.

Receipt of an amendment, filed 5/13/04, in which claim 25 was amended and claims 28-40 were added is acknowledged. Claims 15-40 are pending in the instant application.

Any rejection of record in the previous office actions not addressed herein is withdrawn. Applicants' amendment of the claims has obviated the outstanding grounds of rejection over the prior art. New grounds of rejection are presented herein that were necessitated by applicants' amendment of the claims in the papers filed 5/13/2004.

Information Disclosure Statement

Receipt of an information disclosure statement (IDS), filed on 7/6/1999 is acknowledged. The signed and initialed PTO 1449 has been mailed with this office action.

Drawings

The drawings were received on 5/13/04.

The drawings are objected to because figures 3A-F, 4A-F, and 5C-D contain photographs that did not reproduce well and which are illegible. Corrected drawing sheets are required in

reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

In addition to Replacement Sheets containing the corrected drawing figure(s), applicant is required to submit a marked-up copy of each Replacement Sheet including annotations indicating the changes made to the previous version. The marked-up copy must be clearly labeled as "Annotated Marked-up Drawings" and must be presented in the amendment or remarks section that explains the change(s) to the drawings. See 37 CFR 1.121(d). Failure to timely submit the proposed drawing and marked-up copy will result in the abandonment of the application.

Claim Objections

Applicant is advised that should claims 16-24 be found allowable, claims 30-38 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 30 is an exact duplicate of claim 16 and depends from claim 25. Therefore, claims 30-38 are duplicates of claims 16-24. Applicant can cancel claims 30-38 or amend claim 30 to depend from claim other than claim 25.

Claim 39 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 39 recites, "wherein the gene of interest is selected from the coup consisting of cytokines or costimulatory molecules," and depends from claim 38, which recites, "wherein the cytotoxin contains at least Domain III of *Pseudomonas exotoxin A*." The broad groups of cytokines and costimulatory molecules do not further limit the specific cytotoxin of claim 38.

Claims 18 and 32 are objected to because of the following informalities: the word "cassettes" is plural and should be singular. Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: the specification contains typographical errors. Page 3, lines 9-10 should read "for [examle] example", page 7, line 11 should read "the gene would [be express] encode", and page 7, line 14 should read "operably [leaked] linked." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 34 are vague and indefinite in that the metes and bounds of the term "dominant negative mutant" are unclear. The term is unclear in that the gene containing the mutation is not specified. Therefore, it is not clear what the dominant negative mutant is, or under what conditions the dominant negative mutant functions. It would be remedial to amend the claim language to either remove the term "dominant negative mutant" or indicate the identity of the gene that contains a dominant negative mutation.

Claims 25 and 28 are vague and indefinite in that the metes and bounds of the phrases "a cellular product, a positive potentiator" and "a cellular product, a negative potentiator" are unclear. The phrases are unclear in that the claim may be interpreted to include a cellular product and a positive/negative potentiator. Alternatively, the claim may be interpreted as a

cellular product that is a positive/negative potentiator. It would be remedial to amend the claim to include the phrases "a cellular product that is a positive potentiator" and "a cellular product that is a negative potentiator."

Claims 25 and 28 are vague and indefinite in that the metes and bounds of the term "selectively expressing" are unclear. The term "selectively expressing" implies a positive action step such as the addition of an inducing agent. Upon examination of the specification, it appears that the transduction of a cassette comprising an E2F responsive promoter operably linked to a gene of interest will result in the expression of the gene of interest without additional step (i.e. the malignant cell is competent to express the gene of interest). It would be remedial to amend the claims to combine method steps (c) and (d) to read "waiting until the nucleic acid cassette transduces the malignant cell, causing the E2F responsive promoter to express said gene."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-27 and 30-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 25 is drawn to a method of selectively expressing a gene in a malignant cell. Step (a) of the method requires determining whether the malignant cell expresses sufficient E2F to

cause increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell.

While the specification describes the levels of expression of a heterologous gene driven by an E2F responsive promoter in a C6 glioma cell, mitotically active normal glial cells and mitotically active normal hepatocytes (e.g. Examples, pages 31-36), there is no literal support for method step (a) in the context of the claimed method. There is not a single instance where levels of E2F-dependent gene expression is determined and compared in malignant cells versus non-malignant cells in order to determine an increased level of expression for a gene as part of practicing the recited method.

Moreover, the specification does not provide support for the comparison of a malignant cell to the broad genus of mitotically active non-malignant cells that compose a living organism. Thus, the newly added limitation to claim 25 constitutes new matter.

Claims 28, 29 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 28 is drawn to a method of selectively expressing a gene in a malignant cell relative to a non-malignant cell. Step (a) of the method requires determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter to result in

expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter.

The specification describes methods of comparing expression of a heterologous gene when the gene is operably linked to either an E2F promoter or a constitutive promoter such as the CMV promoter (e.g. pages 7, 9 and 10). The heterologous gene can be either a thymidine kinase (tk) gene or a marker gene such as the *E.* coli β-galactosidase gene (e.g. pages 7 and 9). Further, the specification describes the level of expression achieved by the E2F promoter in a malignant cell as compared to the level of expression observed with the CMV promoter as the following:

> We have found that similar levels of expression of a suicide gene such as the herpes thymidine kinase (tk) gene are obtained in malignant cells whether the gene is operably leaked to a E2F responsive promoter or another promoter such as the cytomegalovirus early promoter (CMV).

The specification does not describe an E2F promoter, malignant cell type and a constitutive promoter where the level of expression directed by an E2F promoter is higher than the level of expression directed by a constitutive promoter. Thus, the newly added claim 28 constitutes new matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims are drawn to methods of selectively expressing a gene in a malignant cell comprising a first step of (i) determining whether the malignant cell expresses sufficient E2F to cause increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell, or (ii) determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter to result in expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter. The remaining method steps comprise adding an effective amount of a nucleic acid cassette to the malignant cell that was determined to express sufficient E2F, and waiting until the nucleic acid cassette transduces the malignant cell causing the E2F responsive promoter to express the gene encoded by the nucleic acid cassette. The nucleic acid cassette comprises an E2F responsive promoter operably linked to a gene of interest wherein said gene encodes a protein that stimulates production or expression of a cellular product that is a positive potentiator or encodes a gene that inhibits production or expression of a cellular product that is a negative potentiator. In the absence of specific and explicit guidance from the specification, a reasonably broad interpretation of claim language is that the claim encompasses embodiments where the cellular product is a compound or molecule that can be found, even transiently, in the cell.

Claims 15, 25, 28, 29 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Weintraub et al (Nature, Vol. 358, pages 259-261, 1992; see the entire reference).

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell

as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells. Further, Weintraub et al teach that the level of expression from the E2F responsive promoter is greater than the expression of the constitutive promoter in malignant cells as compared to mitotically active non-malignant cells. Next, Weintraub et al transfect the pTA-ATF-E2F-CAT plasmid into C33A cells, wait until the CAT gene is expressed from the E2F responsive promoter and determine the levels of chloramphenicol acetyl transferase present in the cell by quantitating the formation of acetylated chloramphenicol from chloramphenicol and acetyl-CoA (i.e. positive potentiation of cellular products) (e.g. Figure 3; Figure 1 Legend).

Thus, each and every one of the limitations recited by the rejected claims are taught by Weintraub et al. However, in the event that one does not interpret the limitations of part (b) of the rejected claim to encompass the reaction products catalyzed by the CAT enzyme, the following rejection is made under 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15, 16, 19-23, 25, 28-30, 33-37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (WO 94/18992, of record; see the entire reference) in view of Weintraub et al (Nature, Vol. 358, pages 259-261, 1992; see the entire reference).

McCormick teaches methods for selectively ablating neoplastic cells or detecting cells lacking p53 and/or RB function by (i) infecting the neoplastic cells with a recombinant virus such as an adenovirus, which is substantially replication deficient in non-neoplastic cells and exhibits at least a partial replication phenotype neoplastic cells, and (ii) expressing a cytotoxic gene, a negative selectable drug gene or a marker gene where expression is correlated with the viral replication phenotype (e.g. Abstract; page 4, lines 23-38; page 5, lines 1-6; page 28, lines 3-10). In one embodiment, a replication deficient adenovirus is administered to a cell population comprising neoplastic cells (e.g. page 6, lines 4-10). The malignant cells described by McCormick include cells such as the osteosarcoma cell line SAOS-2, the osteosarcoma cell line U-2OS, the adenocarcinoma cell line HS700T, and the colon adenocarcinoma cell line DLD-1 (e.g. page 32, lines 5-21). Further, McCormick teaches the administration of the disclosed adenoviral vectors to a tumor mass by direct injection (e.g. page 28, lines 13-19; page 29, line 7). Moreover, the recombinant adenovirus may contain a negative selectable gene such as an HSV tk gene operably linked to an early region enhancer/promoter such as the E2 promoter, so that the negative selectable gene is preferentially transcribed in infected cells which express a replication phenotype (i.e. neoplastic cells) (e.g. page 7, lines 6-15). McCormick teaches the use of the E2 promoter as an especially preferred embodiment, because the E2 promoter contains multiple E2F sites; therefore $RB^{(-)}$ and $p53^{(-)}RB^{(-)}$ cells that lack RB function presumably will exhibit more efficient transcription from the E2 promoter (e.g. page 27, lines 2-22).

McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active

non-malignant cell, or to result in the expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter.

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells. Further, the experiments determine that the level of expression from the E2F responsive promoter is greater than the expression of the constitutive promoter in malignant cells as compared to mitotically active non-malignant cells.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in $RB^{(-)}$ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell. The skilled artisan would have been motivated to make such an addition to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells and is dependent upon increased E2F activity. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of McCormick et al to include the method taught by Weintraub et al.

Claims 15, 16, 19-30, 33-38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick in view of Weintraub et al further in view of Barber et al (US Patent No. 6,310,045, of record; see the entire reference).

The teachings of each of the McCormick and et al references are described above and are applied as before, except:

The McCormick reference teaches a method of transducing neoplastic cells with an adenoviral vector comprising a gene of interest operably linked to an E2 promoter, wherein the

gene of interest is a cytotoxin or a suicide gene such as the HSV tk gene. McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell, or to result in the expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter. McCormick does not teach the use of a cytokine, costimulatory molecule or the *Pseudomonas* exotoxin A domain III.

The Weintraub reference teaches a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell, or to result in the expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter. Weintraub et al does not teach the use of a cytokine, costimulatory molecule or the *Pseudomonas* exotoxin A domain III.

Barber et al teach the use of viral vector constructs that direct the expression of an immune activator or a tumor proliferation inhibitor in a tumor cell (e.g. Abstract; column 2, lines 40-67; column 10, lines 48-67). Barber et al describe representative examples of immune activators, including modulators such as CD3, ICAM-1 and LFA-1 and lymphokines such as tumor necrosis factor, and interleukins 1 through 11 (e.g. column 6, lines 65-58). Further, Barber et al describe tumor proliferation inhibitors such as the HSV tk gene and *Pseudomonas* exotoxin A domain III (e.g. column 6, lines 59-67; column 7, lines 1-20).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in $RB^{(-)}$ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell. Further, it would have been obvious to one of ordinary skill in the art to use a gene encoding *Psuedomonas* Exotoxin A domain III taught by Barber et al as the gene operably linked to the E2F responsive promoter, because McCormick teaches the use of a cytotoxin to ablate cancer cells. The skilled artisan would have been motivated to make such modifications to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells and McCormick teaches the ablation of cancer cells using genes such as a cytotoxin gene but does not describe specific examples. Therefore, one of skill in the art would have been motivated to use either the cytokines, costimulatory molecules or the *Pseudomonas* exotoxin A domain III, since Barber et al teach the utility of the toxin for the ablation of cancer cells. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of McCormick et al to include the method taught by Weintraub et al and the cytokines, costimulatory molecules or *Pseudomonas* exotoxin A domain III taught by Barber et al.

Claims 16-18, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick in view of Weintraub et al further in view of Raj et al (Oncogene, Vol. 12, pages 1279-1288, 1996; see the entire reference).

The McCormick reference teaches a method of transducing neoplastic cells with an adenoviral vector comprising a gene of interest operably linked to an E2 promoter. Further, McCormick teaches the use of other promoters and/or enhancers (e.g. page 27, lines 2-10). McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell. McCormick does not teach the various E2F responsive promoters, or that the malignant cell may be a glioma.

The Weintraub reference teaches a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell. Weintraub et al does not teach the various E2F responsive promoters, or that the malignant cell may be a glioma.

Raj et al teach the various E2F responsive promoters (e.g. page 1279, column 2). Further, the various promoters directed expression of a reporter gene in the human glioma cell line U-87MG (e.g. Table 2). The expression showed a dose-dependent increase upon addition of the pCMV-E2F expression plasmid to the transfection (e.g. Figure $5B_1$).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell,

and the method taught by Raj et al to determine the E2F activity in a glioma cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in $RB^{(-)}$ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell. Further, it would have been obvious to one of ordinary skill in the art to use the various E2F responsive promoters taught by Raj et al, because McCormick teaches the use of an E2F responsive promoter or other various promoters. The skilled artisan would have been motivated to make such modifications to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells and McCormick teaches the use of various promoters in the viral expression vector, and because Raj et al teach varying levels of expression from the E2F responsive promoters. The variable level of promoter activity would allow one skilled in the art to vary the level of a cytotoxin or suicide gene to modulate the cytotoxic effect. Therefore, one of skill in the art would have been motivated to modify the methods of McCormick to include the methods of Weintraub et al and Raj et al and the promoters of Raj et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of McCormick et al to include the methods taught by Weintraub et al and Raj et al and the promoters taught by Raj et al.

Conclusion

No claims are allowed. Claims 15-40 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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GERRY LEFFERS
PRIMARY EXAMINER

Jennifer Dunston
Examiner
Art Unit 1636

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